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TITLE: Non-Uniformly Sampled MR Correlated Spectroscopic Imaging in Breast Cancer and Nonlinear Reconstruction

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CONTRACTING ORGANIZATION: UCLA Geffen School of Medicine, Los Angeles, CA

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13. SUPPLEMENTARY NOTES

14. ABSTRACT **Purpose**: i) Non-uniform sampling (NUS) schemes will be combined with 5D EP-COSI sequence. ii) GS-based CS reconstruction schemes will be developed for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better reliability . iii) Alterations in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women which will improve the diagnostic accuracy. The study patient cohort will include 50 patients with malignant breast carcinoma, 20 patients with benign breast tumor and 20 healthy women.
Scope: To demonstrate improved MR spectroscopic imaging techniques will enable unambiguous measurement of metabolites and lipids in situ, which could potentially complement the existing diagnostic modalities commonly used in breast carcinoma. Also, monitoring glycine, taurine and myo-inositol may play a role in breast cancer therapeutic validations.
Major finding: Successful Implementation of a novel 5D EP-COSI, novel reconstruction using GS and its correlation with DWI-MRI for evaluation in 32 malignant and 17 benign breast cancer patients, and 19 healthy women, using a 3T MRI scanner. The 5D EP-COSI data showed novel metabolite changes in addition to water, and DWI images showed reduced ADC values in suspicious lesions of breast cancer patients compared to healthy women. Novel biomarker detection of glycine, myo-inositol in vivo was achieved using 5D EP-COSI. Further acceleration may enable shorter acquisition in 15 minutes or so.

15. SUBJECT TERMS MR Spectroscopy (MRS), echo-planar imaging based correlated spectroscopic imaging (EP-COSI), five-dimensional (5D), two-dimensional (2D), group sparsity (GS), compressed sensing (CS), apparent diffusion coefficient (ADC), dynamic contrast enhanced (DCE) MRI,

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TABLE OF CONTENTS

1. Introduction: Breast cancer death rates are higher than those for any other cancer, besides lung cancer in US. More than 232,670 new cases are diagnosed annually. Diagnostic accuracy and effective therapeutic management of the breast tumor remain significant medical challenges, hence early detection, diagnosis, and timely treatments are essential to successful health care. Currently, histological classification from biopsy specimens is generally used as the gold standard to determine malignancy. Hence, optimal imaging methods will enable predicting whether a tumor is going to behave in a benign or aggressive fashion. The proposed Breakthrough Step I grant application will focus on three specific goals: 1) To implement and optimize the NUS based 5D EP-COSI sequence on a 3T Prisma MRI scanner to accelerate the acquisition by an order of magnitude. 2) To develop GS- and total variation (TV)- based CS reconstruction schemes for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better fidelity. 3) To record changes in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women to improve the diagnostic accuracy. Next to lung cancer, breast cancer is the leading cause of death in women in the US. Improving the specificity of malignant and benign tumors using accelerated MRSI techniques will be a major outcome. Compressed sensing (CS)-based multi-dimensional magnetic resonance spectroscopic imaging (MRSI) will significantly increase the speed of data acquisition with minimal discomfort for breast cancer patients leading to improved diagnostic accuracy and early detection. In this proposal, we will develop a novel technique for identifying breast cancers more robustly and with greater accuracy than methods currently available.

2. Keywords: MR Spectroscopy (MRS), echo-planar correlated spectroscopic imaging (EP-COSI), non-uniform undersampling (NUS), compressed sensing (CS), five-dimensional (5D), two-dimensional (2D), Group sparsity (GS), compressed sensing (CS), total variation (TV), dynamic contrast enhanced (DCE) MRI, apparent diffusion coefficient (ADC).

3. Accomplishments:

Three major goals are the following**: 1**) To further optimize a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the Siemens IDEA compiler running on the latest VD13D platform). **2**) To implement and optimize non-linear reconstruction methods such as group sparsity and total variation. **3**) To record i) the 5D NUS EP-COSI data, and ii) DWI and to evaluate ADC maps in the malignant and benign breasts, and healthy women and to correlate the MRSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of multi-voxel based 2D MRS and DWI data to differentiate benign from malignant tumors.

What was accomplished Under these goals:

To accomplish the above mentioned goals, the following ten tasks were proposed:

Task 1: To implement and evaluate a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the latest Siemens IDEA compiler running on the latest VE11 platform). (**Months 1-6**).

The 5D EP-COSI sequence as shown in Fig.1 was implemented using the Idea C++ compiler in three different platforms (Siemens VE11A, VE11B and VE11C): top row: the analog-to-digital converter (ADC); 2nd row: the radio-frequency (RF) wave forms used to the slice localization along 3 spatial dimensions; 3rd through 5th rows represent X, Y and Z gradient wave forms.

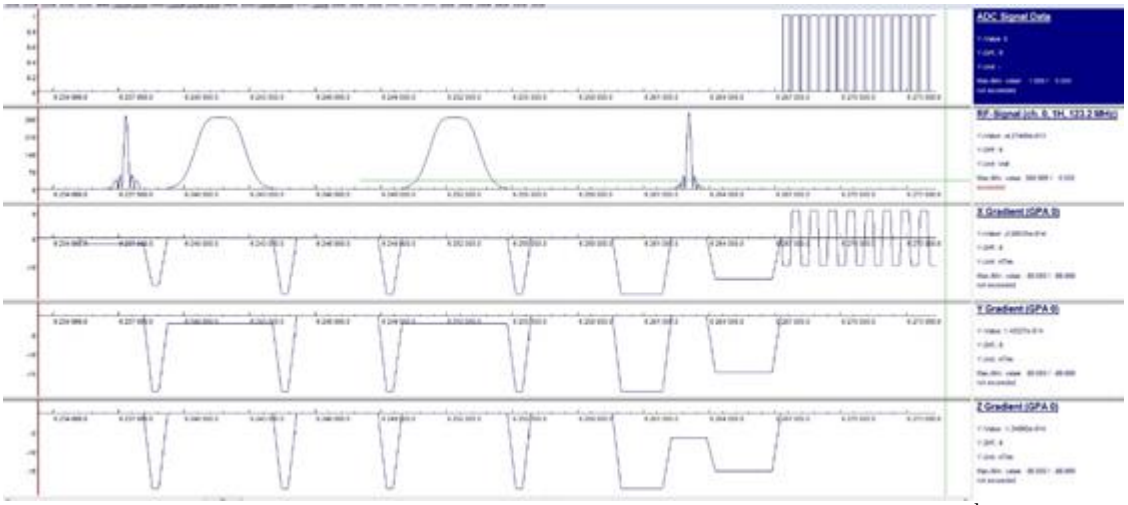


Fig.1. The 5D EP-COSI sequence showing the ADC (top row), RF (2nd row) and gradient waveforms (3rd through 5 rows).

Task 2: To evaluate the accelerated 5D EP-COSI data using a breast phantom containing two concentric spheres, the inner one containing several metabolites (choline and ethanolamine groups, creatine, lactate and more amino acids) which have been reported in breast tissues surrounded by the outer phantom containing corn oil to mimic fatty tissues known to be in breast tissues, and to optimize the echo speed-factor and other acquisition parameters using the phantom (**Months 1-6**).

As shown in Fig.2, we prepared a corn oil phantom (left) containing saturated and unsaturated lipids to mimic infiltrating fit in the breast tissue and a quad phantom (right) containing N-acetylaspartate, lactate, creatine and choline. Eight slices from the oil phantom localized by the 5D EP-COSI sequence is shown on the left and similarly, 8 slices from the quad phantom on the right side. Extracted 2D COSY spectra from the corn oil and lactate are also shown.

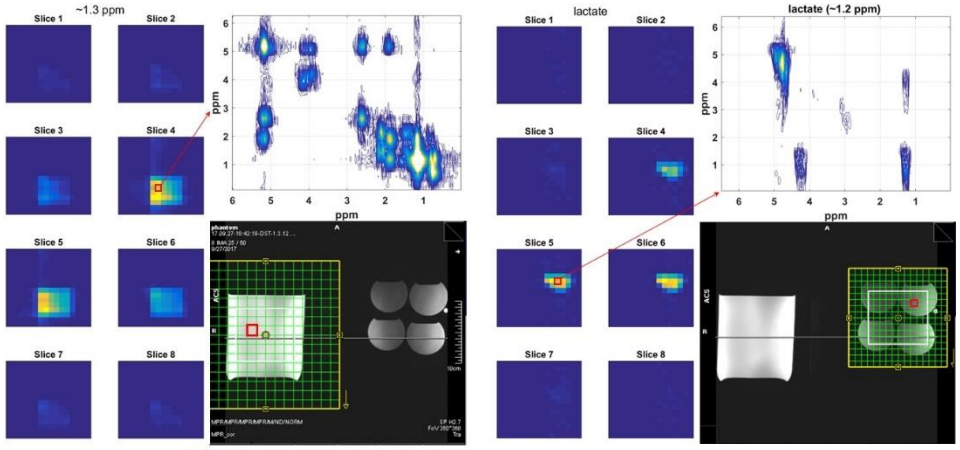


Fig.2. A corn oil and a quad phantom containing metabolites are shown.

Task 3: To implement and optimize non-linear reconstruction methods (group sparsity and total variation). (**Months 3-9**).

Using the above corn oil and the metabolite (quad) phantoms, the undersampled data at 8X, 12X and 16X were reconstructed using two different non-linear reconstruction methods: 1) total variation (TV) and 2) group sparsity (GS). The GS method was able to retain the fidelity even at higher acceleration schemes (12X and 16X).

Task 4: To continue to evaluate/optimize the accelerated 5D EP-COSI data using the breast phantom containing two concentric spheres, to optimize the echo speed-factor and other acquisition parameters using the phantom (**Months 7-18**).

We have purchased a spherical flask containing two layers in which the corn oil will be inside one layer and breast metabolites (choline, phosphoryl and glycerylphosphoryl choline, uridine phosphate) from Sigma-Alrich.

We plan to acquire the 5D EP-COSI data to investigate the contamination of lipids (corn oil). Due to the Covid-19 related shut-down from March 2020, we have been unable to acquire this data so far. Alternately, a phantom containing metabolites in 80% of 1 1liter spherical flask and corn oil on the top was also investigated.

Task 5: To record the 5D EP-COSI spectra in the fatty, glandular and ductal areas of healthy breasts. Twenty healthy female volunteers (25-70 years old) with no previous history of breast cancer will be investigated. (**Months 9-60**).

As shown in Fig.3, the accelerated (8X) 5D EP-COSI data was acquired in a healthy subject and the reconstructed data using TV and GS are shown. The chemical shift multi-slice images were of good quality using both reconstruction methods.

(A) (B)

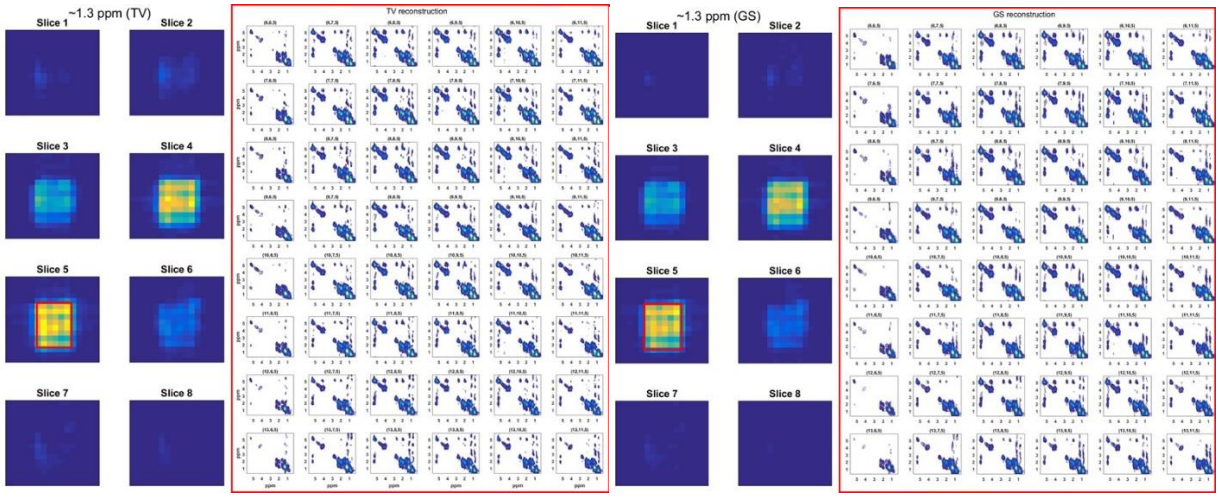


Fig.3. Accelerated 5D EP-COSI data acquired in a healthy volunteer and reconstructed using TV (A) and GS (B)

Twenty healthy women (age range of 26-64 years) were screened for the MRI scans. One subject declined to continue with the scan due to claustrophobia and a second subject was excluded due to not meeting the criteria. Hence, the 5D EP-COSI data have been successfully scanned in 18 healthy using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 6: To record multi-slice DWI in twenty healthy breasts, and to calculate the ADC maps. (**Months 9-60**).

Diffusion weighted MRI data have been successfully recorded in 18 healthy subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 7: To record the 5D EP-COSI spectra in twenty patients with benign breast tumor (fibroadenoma, proliferative fibrocystic change and papillomas) (**Months 9-60**).

The 5D EP-COSI and diffusion weighted MRI data have been successfully scanned in 18 benign breast cancer subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform. Shown in Fig.4 are results from a benign breast cancer subject.

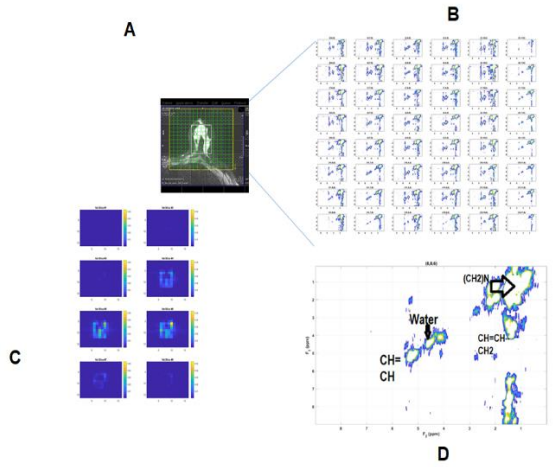


Fig.4. Accelerated (8X faster) 5D EP-COSI data acquired in a 32 yo benign (fibroadenoma) breast cancer subject and reconstructed using GS: A) Axial MRI showing the FOV covered by 5D EP-COSI. B) Multi-voxel COSY spectra over the volume localized by the 5D EP-COSI sequence. C) 8 Slice-chemical shift Images of the polymethylene $(CH2)_N$ resonance at 1.4ppm. D) 2D COSY spectrum extracted from the location (8,8) of the 6th slice.

Task 8: To record the 5D EP-COSI spectra in fifty patients with biopsy-proven breast cancer (invasive carcinoma, ductal carcinoma in situ and invasive lobular cancer) (**Months 9-60**).
Thirty one malignant breast cancer patients were investigated so far. The 5D EP-COSI acquisition was terminated in two malignant breast cancer patients either due to multiple clips from biopsy or subject's refusal to continue with the scan. Due to the covid-19 shut-down, we were unable to recruit the proposed total of 50 malignant patients.

Results from a 41 y.o. malignant breast cancer patient is shown in Fig.5.

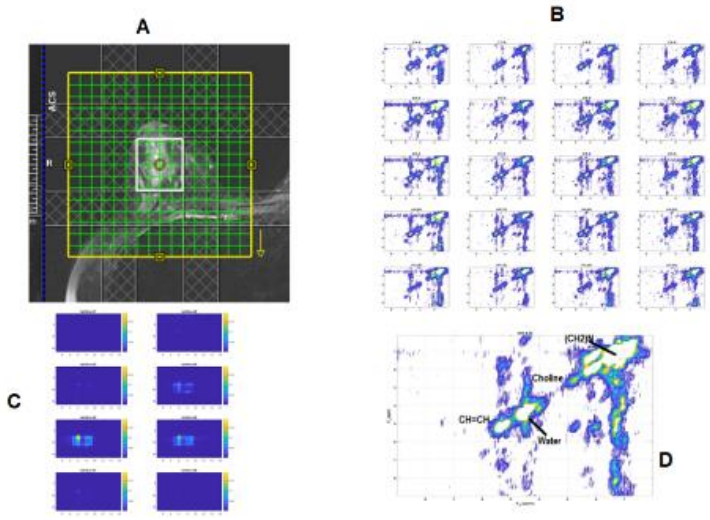


Fig.5. Accelerated 5D EP-COSI data (8X faster) acquired in a 41 yo malignant breast cancer patient (grade 3, invasive ductal carcinoma and ductal carcinoma in situ) and reconstructed using GS: A) Axial MRI showing the field of view (FOV) covered (yellow boundary) and the 3spatial dimensions localized by the white box. B) Multi-voxel COSY spectra (1cm x1cm x1.5cm) over the volume localized by the 5D EP-COSI sequence. C) 8 Slice-chemical shift Images of the polymethylene $(CH2)_N$ resonance at 1.4ppm . D) 2D COSY spectrum extracted from the location (10,8) of the 5th slice.

Shown in Fig.6 through Fig.7 are extracted 2D COSY spectra (3.4ml) acquired in malignant and benign breast cancer patients using 5D EP-COSI.

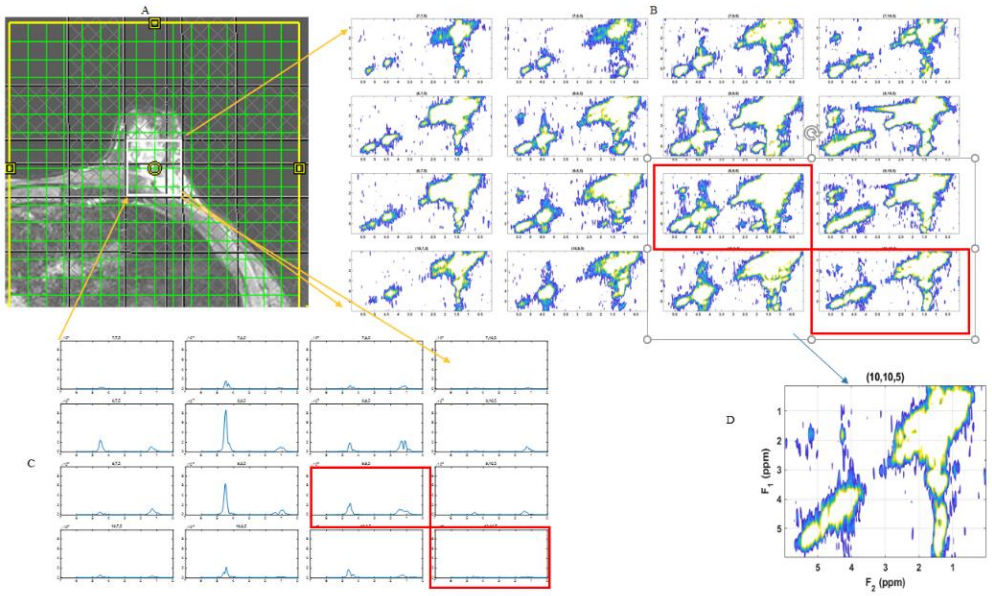


Figure 6: Accelerated 5D EP-COSI data (8X faster) acquired in a 51 yo malignant breast cancer patient (grade 3, invasive ductal carcinoma in situ) and reconstructed using GS: A) Axial MRI showing the field of view (FOV) covered (yellow boundary) and the 3spatial dimensions localized by the white box. B) Multi-voxel COSY spectra (1cm x1cm x1.5cm) over the volume localized by the 5D EP-COSI sequence. C) Multi-voxel 1D PRESS spectra (1cm x1cm x1.5cm) over the volume localized by the 5D EP-COSI sequence where only one increment was used for the 2nd spectral dimension. D) 2D COSY spectrum extracted from the location (10,10) of the 5th slice.

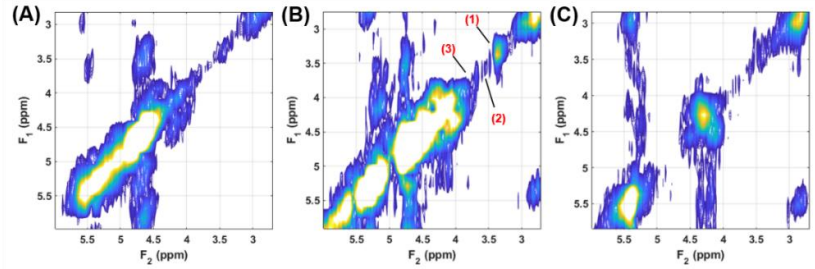
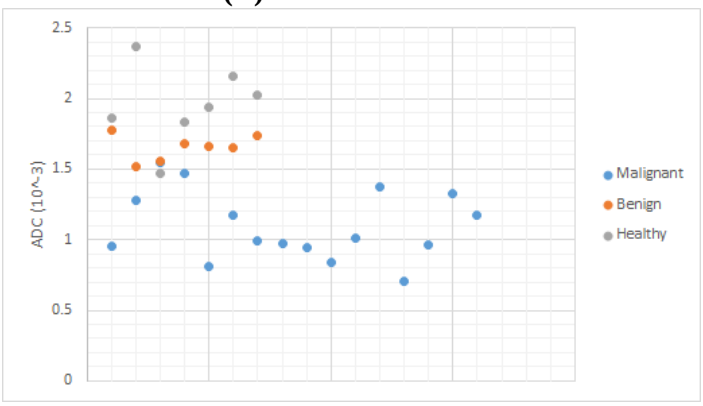


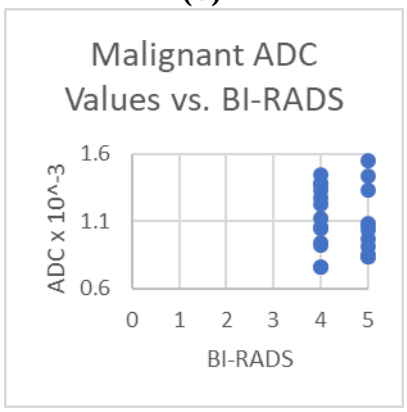
Figure 7. Extracted COSY spectra from voxels within the tumor regions of 3 malignant patients (A) – (C). The F_1-F_2 ppm range is expanded to within 2.7 – 6 ppm. The peak regions labeled (1), (2), and (3) are those corresponding to metabolites such as choline, taurine and myo-inositol/glycine.

Task 9: To record multi-slice DWI in fifty malignant patients with biopsy-proven breast cancer and twenty benign breast cancer, and to calculate the ADC maps. (**Months 9-60**).
DWI was also recorded in thirtyone malignant breast cancer patients and we have been quantifying the apparent diffusion coefficient (ADC) using the DWI data. Shown in Fig.8 are ADC values in 3 subject groups (A) and ADC values with respect to tumor grades (B) in malignant patients.

Figure.8: A) ADC (10^{-3} mm^2/sec) values quantified in malignant and breast cancer patients, and healthy women using DWI. **B**) Plots showing ADC values versus BIRAD scores.

(A) **(B)**





Task 10: To correlate the accelerated 5D EP-COSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of the MRSI and DWI data in differentiating benign from malignant tumors. (**Months 12-60**).
We have studied a total of 31 malignant and 17 benign breast cancer patients and 18 healthy women successfully. Both 5D EP-COSI and DWI data have been recorded, and post-processing of the entire data is being analyzed now. Due to the covid-19 shutdown, the students who were assisting me with the data analysis were asked to stay home and the data processing. Dr. James Sayre is currently performing the statistical analysis over the breast imaging data which will be included in an invited manuscript to be submitted to the British J Radiology Open in February 2022.

Conclusions: 1) Successful implementation and evaluation of 5D EP-COSI sequence (3 spatial and 2 spectral dimensions) in breast cancer for the first time. 2) The 5D EP-COSI and DWI data were successfully acquired in 29 malignant, 17 benign and 18 healthy women. Due to Covid-19 shutdown, we were unable to reach the targeted total of 50 malignant patients; however, we were able to investigate the targeted healthy and benign subjects. 3) In addition to choline molecules (glycerylphosphocholine, phosphocholine and free choline) what have been reported in malignant breast cancer patients, we were able to detect new biomarkers such as glycine, myo-inositol and more. 4) Role of glycine and myo-inositol in therapeutic evaluation of breast cancer needs further investigation.

Key Research Outcomes:

- The accelerated 5D EP-COSI acquisition and non-linear reconstruction using Group Sparsity and Total Variation.
- The 5D data has been successfully evaluated in 19 healthy women, 17benign and 32 malignant breast cancer patients so far using the UCLA Radiology Siemens 3T Skyra MRI scanner equipped with a dedicated breast phased-array assembly.
- As summarized in the previous year reports, this sequence is available now at UCLA only and is not supplied by any of MRI manufacturers.
- Research agreements were signed to share this sequence with researchers outside UCLA.
- The DWI-MRI protocol was also successfully evaluated in a total of 19 healthy women, 17 benign and 32 malignant breast cancer patients.
- As proposed in our BCRP, Breakthrough Award Level 1 grant, our pilot results clearly demonstrate that the accelerated 5D EP-COSI spectroscopic imaging sequence can be combined with a clinical breast DWI protocol with the total duration of less than an hour.
- The protocol is completely safe enough to be included in any MRI protocol to be evaluated in breast cancer for improving the overall specificity.
- A manuscript including the 5D EP-COSI and DWI data is being prepared and will be submitted to British J Radiology Open as an invited manuscript in February 2022.

What Opportunities for training and professional development has the project provided?: Mr. Andres Saucedo, a Ph.D. student working in the group of Dr. Thomas, has received the required safety training to run the MRI and MR spectroscopy protocol. He has recorded MRI, DWI and 5D EP-COSI in malignant and benign breast cancer patients, and healthy women using the 3T MRI scanner (Siemens Skyra).

How were the results disseminated to communities of interest: Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?: The grant has ended on Sep.29, 2021.

4. Impact:
What was the impact on the development of the principal disciplines of the project?: Nothing to Report
What was the impact on other disciplines? Nothing to Report
What was the impact on technology transfer? Nothing to Report
What was the impact on society beyond science and technology? Nothing to Report

5. Changes/Problems: Nothing to Report

6. Products:
Publications, Conference papers and Presentations: Two abstracts were presented as ePoster presentations at the 2019 International Society of Magnetic Resonance in Medicine, May 11-26, Montreal, Canada:
1) Saucedo A, et al. "Detection of Choline, Glycine and Myo-inositol in Malignant Breast Cancer *In-vivo* Using Multi-dimensional Spectroscopic Imaging"
2) Saucedo et al. "Apparent Diffusion Coefficient Using Diffusion Weighted MRI and Biochemical Correlates in Human Breast Cancer"
3) Thomas MA. "MR Spectroscopic Imaging", invited talk at the 2021 International Society of Magnetic Resonance in Medicine (ISMRM) virtual Conference.
4) Joy et al. "Accelerated Spectroscopic Imaging in Breast Cancer and Correlation with Diffusion Weighted Imaging Findings", British J Radiology Open (To be submitted in Feb.2022)

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name	**M. Albert Thomas Ph.D.**
Project Role	P.I.

Researcher Identifier	0000-0001-9037-2585
Nearest person month worked	5 months
Contribution to Project	Design of the project and supervision of the MRI data acquisition and pos-processing
Funding Support	Dr. Thomas is currently funded by NIH grants also
Name	**Melissa Joines M.D.**
Project Role	Co.I.
Researcher Identifier	None
Nearest person month worked	1 months
Contribution to Project	Study Subject Recruitment and review of MRI
Funding Support	None
Name	**Stephanie Lee-Felker M.D.**
Project Role	Co.I.
Researcher Identifier	None
Nearest person month worked	1 months
Contribution to Project	Study Subject Recruitment and review of MRI
Funding Support	None
Name	**Manoj Sarma**
Project Role	Co-I
Nearest person month worked	4 months
Contribution to Project	Sequence Development and Data Processing
Funding Support	Partly funded by NIH grants also
Name	**Andres Saucedo M.S.**
Project Role	Graduate Student Researcher
Research Identifier	None
Nearest person month worked	9 months
Contribution to Project	Data Acquisition and Post-processing
Funding support	funded by the current DOD grant
Name	**Victoria Rueda B.S.**
Project Role	Study Coordinator
Nearest person month worked	3 months
Contribution to Project	IRB protocol renewal/amendment, recruitment
Funding Support	Radiology Departmental funds also
Name	**Sumit Kumar**
Project Role	Student Researcher
Nearest person month worked	1 months
Contribution to Project	Data Post-processing
Funding Support	funded by the current DOD grant
Name	**Daniel Kohanghadosh**
Project Role	Student Researcher
Nearest person month worked	2 months
Contribution to Project	Data Processing
Funding Support	funded by the current DOD grant
Name	**Stephanie Jane Marks**
Project Role	Study Coordinator
Nearest person month worked	1 months

Contribution to Project	IRB protocol submission, recruitment
Funding Support	Departmental support also

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to Report
What other organizations were involved as partners? Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS: Nothing to Report

9. Appendices:
1) Saucedo A, et al. Detection of Choline, Glycine and Myo-inositol in Malignant Breast Cancer *In-vivo* Using Multi-dimensional Spectroscopic Imaging, 2019 International Society of Magnetic Resonance in Medicine, May 11-26, Montreal, Canada.
2) Saucedo et al. Apparent Diffusion Coefficient Using Diffusion Weighted MRI and Biochemical Correlates in Human Breast Cancer, 2019 International Society of Magnetic Resonance in Medicine, May 11-26, Montreal, Canada

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Detection of Choline, Glycine and Myo-inositol in Malignant Breast Cancer In-vivo Using Multi-dimensional Spectroscopic Imaging

Andres Saucedo[1], Manoj Kumar Sarma[1], Sumit Kumar[1], Kavya Umachandran[1], Melissa Joines[1], Stephanie Lee-Felker[1], Maggie DiNome[2], and Michael Albert Thomas[1]

[1]Radiological Sciences, University of California, Los Angeles, Los Angeles, CA, United States, [2]Surgery, University of California, Los Angeles, Los Angeles, CA, United States

Synopsis

Multi-parametric MR techniques have been used to diagnose and monitor the therapeutic outcome of cancer in the breast and other tissues and organs. One-dimensional MRSI has shown significantly elevated choline and higher water-to-fat ratio in malignant tumors as compared to healthy controls. Two-dimensional MRS resolves peaks along an additional spectral dimension which overcomes the overlap limitation of 1D MRSI, thereby providing more discriminatory information for developing non-invasive methods for cancer grade determination. This study presents the first application of an accelerated, echo-planar based technique that acquires correlated (2D) spectroscopy data for each voxel of 1.5ml resolution within a 3D volume (5D EP-COSI) in breast cancer. Our preliminary results in a pilot cohort of malignant and breast cancer patients demonstrate changes in unsaturated fatty acids and increased choline in malignant group compared to benign and healthy women. These pilot results indicate the potential application of the 5D EP-COSI technique which may be useful in improving the specificity of breast cancer.

Introduction

Magnetic resonance imaging and spectroscopy (MRI/MRS) have been applied to diagnose and monitor the therapeutic outcome of cancer in the breast and other tissues and organs. Dynamic contrast-enhanced (DCE)-MRI has high sensitivity in detecting the presence of cancerous lesions, however the addition of magnetic resonance spectroscopic imaging (MRSI) greatly improves the specificity of diagnosis[1-4]. One-dimensional MRSI has shown significantly elevated choline and higher water-to-fat ratio in malignant tumors as compared to healthy controls. Due to peak overlap in 1D MRS methods, however, the correlation between lipid and other metabolite levels and cancer grade can be obscured. Two-dimensional MRS resolves peak information along an additional spectral dimension which overcomes the overlap limitation of 1D MRSI, thereby providing more discriminatory information for developing non-invasive methods for cancer grade determination. This study presents the first application of an accelerated, echo-planar based technique that acquires correlated (2D) spectroscopy data for each voxel of 1.5ml resolution within a 3D volume (5D EP-COSI)[5-6] in breast cancer.

Methods

Subjects with malignant (n=20, mean age of 53.2 years) and benign (n=11, mean age of 36.7 years) breast cancer as well as 7 healthy volunteers (mean age of 38.7 years) were recruited as part of an IRB-approved study to record 5D EP-COSI data on a 3T scanner with the following parameters: TR = 1.5 s, TE = 35 ms, voxel size = 1.0 × 1.0 × 1.5 cm3, matrix size = 16 × 16 × 8, spectral width SW2 = 1190 Hz, SW1 = 1250 Hz, 512 t2 points, 64 t1 increments. A non-water-suppressed EP-COSI data with t1=1 was also recorded. Both water and non-water-suppressed scans were acquired for a total scan time of 28.8 minutes. The data was non-uniformly undersampled in the ky-kz space and t1 dimensions with an acceleration factor of 8, and reconstructed using Group Sparsity-based compressed sensing[6]. EP-COSI data taken from 12 malignant, 6 benign and 5 healthy cases were considered and compared qualitatively. Voxels corresponding to the tumor region in both benign and malignant cancer patients were determined based on the subtraction images from clinically-obtained DCE-MRI.

Results

The 5D EP-COSI technique records 2D MRS data within multiple slices, allowing for broad coverage of the tumor volume (Figure 1(A)). Figure 1(B) shows the chemical shift image of methylene fat (1.4 ppm) demonstrating localization accuracy. The location of the tumor region from a malignant patient and the corresponding COSY spectra is demonstrated in Figure 2, which shows the presence of elevated choline and water, in contrast to the surrounding region. Malignant and benign tumors both present high water content, though choline is elevated only in malignant cases (Figure 3). Additional metabolites in the 3-4 ppm region, such as myo-Inositol, glycine, and taurine are also measureable (Figure 4). Figure 5(A) shows choline-to-fat ratio (Cho/Fat) as a function of cancer grade among the 12 malignant patients. Cho/Fat ratio was able to distinguish the cancer grades and progressive increase was observed with the increasing grades. Figure 5(B) shows the distribution of Cho/Fat as a function of Ki-67 metric.

Discussion

Our preliminary results in a pilot cohort of malignant and breast cancer patients demonstrate changes in unsaturated fatty acids and increased choline in malignant group compared to benign and healthy women. In contrast, earlier reports using 1D MRS quantified the lipid peak at 1.4ppm only 1-3. Several ex vivo high resolution magic angle spinning (HR-MAS) studies have reported detection of choline, glycine, taurine, myo-inositol and more[7-8]. For the first time, our preliminary multi-dimensional MR Spectroscopic Imaging data has shown the feasibility of detecting many metabolites more than choline similar to reported by ex vivo MRS studies. One of the drawbacks of this study was due to chemical shift displacement errors (CSDE) by using conventional slice-selective 90 degree RF pulses and CSDE may have eliminated detection of uridine diphosphate hexose and other metabolites in the low field region; this can be minimized using adiabatic RF pulses.

Conclusion

Our pilot results indicate the potential application of the 5D EP-COSI technique which may be useful in improving the specificity of breast cancer. Further investigation using a larger cohort of breast cancer patients will be necessary in the future.

Acknowledgements

This research was supported by a CDMRP Breakthrough Step I award #W81XWH-16-1-0524.

References

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Figures

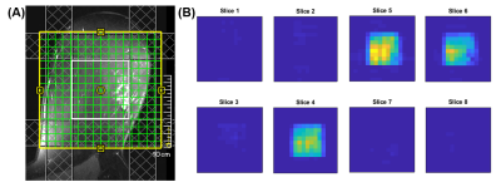

Figure 1: (A) Axial localization of volume of interest (VOI) in malignant breast cancer patient. The hyper-intense region on the right side of the VOI contains higher concentration of water. (B) Chemical shift image of methylene fat (1.4 ppm), showing a hypo-intense region in the water area. Three main central slices contain the highest signal-to-noise ratio (SNR).

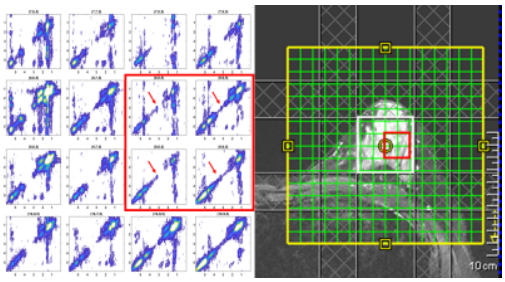

Figure 2: (Left) Multi-voxel COSY spectra of a 45 year-old malignant caner patient in a 4 × 4 tumor region within the volume-of-interest (VOI) (right). Note the elevation of the choline peak and water, which is an indicator of tumor malignancy.

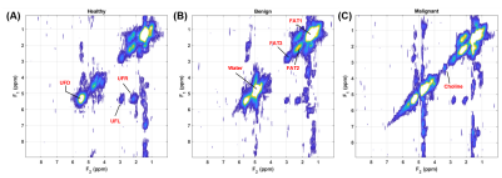

Figure 3: Extracted voxels from (A) a healthy volunteer, (B) a benign lesion, and (C) a malignant tumor. Note the elevation of water in both the benign and malignant cases. Choline is elevated only in the malignant case, while both water and choline are markedly reduced in the healthy COSY spectra. The major lipid peaks are labeled, in which UFD is the olefinic fat at 5.4 ppm, UFL and UFR are the left and right unsaturated fatty acid cross peaks, respectively, FAT1 represents methylene lipids at 1.4 ppm, FAT2 the lipids at 2.1 and FAT3, the methylene lipids at 2.9 ppm.

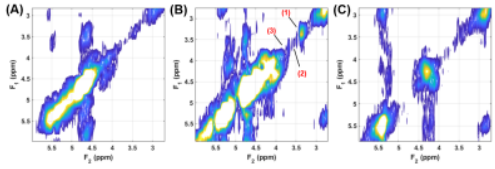

Figure 4: Extracted COSY spectra from voxels within the tumor regions of 3 malignant patients (A) – (C). The F_1-F_2 ppm range is zoomed to within 2.7 – 6 ppm. The peak regions labeled (1), (2), and (3) are those corresponding to the myo-inositol, glycine, and taurine metabolites.

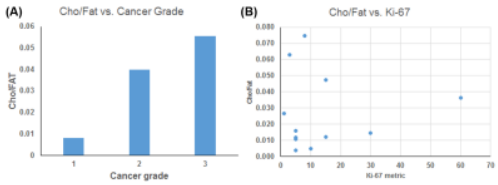

Figure 5: (A) Mean choline-to-fat ratio (Cho/Fat) as a function of cancer grade (B) Cho/Fat and the relationship to the Ki-67 metric (expressed as a percentage), which indicates the degree of severity of the malignant cancer, with 100% being the most severe.

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Apparent Diffusion Coefficient Using Diffusion Weighted MRI and Biochemical Correlates in Human Breast Cancer

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Synopsis

Multiparametric MRI has been investigated in breast and prostate cancer, and other tumors. We evaluated diffusion weighted imaging in a pilot cohort of 20 malignant and 11 benign breast cancer patients, and 7 healthy women. MR spectra were recorded using an accelerated version of five dimensional echo-planar correlated spectroscopic imaging (5D EP-COSI). Significant decline in ADC values of malignant breast cancer compared to benign and healthy women. There was a negative correlation of choline with ADC values in malignant cancer patients. Our findings suggest that choline and lipids can be reliable biomarkers in addition to widely used ADC.

Introduction

During the last three decades, multiparametric MR imaging has been widely investigated in breast cancer[1-3]. Diffusion-weighted imaging (DWI) is one of MRI modalities to differentiate malignant from benign tumors using the DWI metric, namely apparent diffusion coefficient (ADC)[4-8]. The DWI has been widely investigated in breast cancer before and after neoadjuvant chemotherapy. Non-invasive biochemical characterization of metabolites such as choline and lipids has been accomplished in breast cancer using water suppressed MR Spectroscopy (MRS) and changes of choline and lipids in breast cancer has been investigated also using MRS[9-12]. In this project, we investigated DWI and multi-dimensional MR Spectroscopic Imaging (MRSI) in malignant and benign breast cancer patients and also in healthy women.

Materials and Methods

We recruited 20 malignant (mean age of 53.2 years) and 11 benign (mean age of 36.7 years) breast cancer patients and 7 healthy women (mean age of 38.7 years). A 3T MRI scanner equipped with a 15 channel breast phased-array coil was used for this investigation. The DWI acquisition protocol included the following: 2D spin-echo echo-planar imaging (EPI) sequence (TR/TE of 3800/93ms; data matrix, 192 × 192; signal average, 3; slice thickness, 3 mm; distance factor, 20%) in the axial plane. Sensitizing diffusion gradients in three orthogonal directions with b values of 50 and 800 s/mm were applied. The ADC maps were created automatically by the system from the trace-weighted images with b values of 50 and 800 s/mm. The 5D EP-COSI acquisition parameters were as follows: The 5D EP-COSI sequence was home-developed [13] and 8X acceleration was used along ky, kz and t1 dimensions. TR/TE=1.5s/30ms; Field of view (FOV) along the 3 spatial dimensions were 160mmx160mmx120mm with 16-32 along kx, 16 along ky and 8 along kz; A voxel size of approximately 60x60x50mm3 was localized by three slice-selective RF pulses (90^0-180^0-90^0). 2D COSY spectra were extracted from a voxel resolution of 1.5ml. The DWI data was analyzed using the manufacturer supplied software and ADC values were quantified for all groups of subjects. A home-developed Matlab code was used to reconstruct the undersampled 5D EP-COSI data using group sparsity[14].

Results

Shown in Fig.1 are ADC maps derived from the DWI data acquired in a 45 y.o. malignant and 35 y.o. benign breast cancer patients and a 45 y.o. healthy subject. Fig.2 (A) shows mean±SD of ADC values in 15 malignant and 8 benign breast cancer patients, and 7 healthy women. The remaining data in 5 malignant and 3 benign breast cancer patients were excluded due to inferior DWI quality. Fig.2 (B) shows the distribution of ADC values in the three groups. We observed significant reduction of ADC in malignant patients compared to benign (1.1 vs 1.66) and healthy controls (1.1 vs 1.95) with $p<0.001$. Figure 3 shows ADC values versus A) tumor grades and B) MRI tumor sizes in malignant patients. Shown in Fig.4 are multi-voxel COSY spectra recorded in a 40 y.o. malignant breast cancer patient (grade 3, size of 63mm, KI-67 of 20-30%) with the axial T1-weighted MRI showing the MRSI grids. Table 1 shows excellent correlation between the two metrics, namely ADC and choline.

Discussion

Both DWI and 5D EP-COSI data were acquired using the echo-planar read-outs which are sensitive to B0 inhomogeneity leading to artifacts. Our results are in agreement with previous studies on invasive breast cancer[15]. The ADC values of malignant patients were significantly lower than benign and healthy subjects. 2D COSY spectra were extractable from a voxel size of 1.5ml from the 5D EP-COSI data. Strong correlation of choline measured through 5D EP-COSI shows the reliability of spectroscopic data. 5D EP-COSI has the advantage of better coverage of breast tumors compared to other known spectroscopic sequences enhancing the accuracy. Increased ADC and decreased choline in malignant group reflect the increased cellularity[16] of the malignant lesions without the need for the administration of contrast medium. DWI and 5D EP-COSI shows strong potential as an adjunct technique to reduce breast biopsies, and could increase the overall specificity of DCE-MRI.

Conclusion

The pilot findings of this study using DWI and 5D WP-COSI are encouraging and provide positive evidence to support 5D EP-COSI and DWI as useful adjuncts to standard breast MRI protocols in assisting with the diagnosis of breast cancer. However, further validation using a larger cohort of breast cancer patients is needed.

Acknowledgements

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Figures

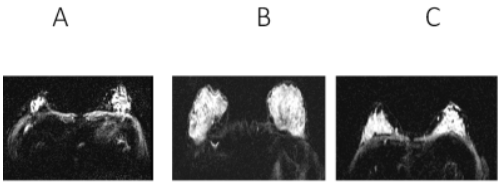

Figure.1: ADC maps of the malignant and benign breast cancer, and healthy subjects. The regions of interest chosen for the analysis are also marked with a circle in malignant and benign breast cancer subjects.

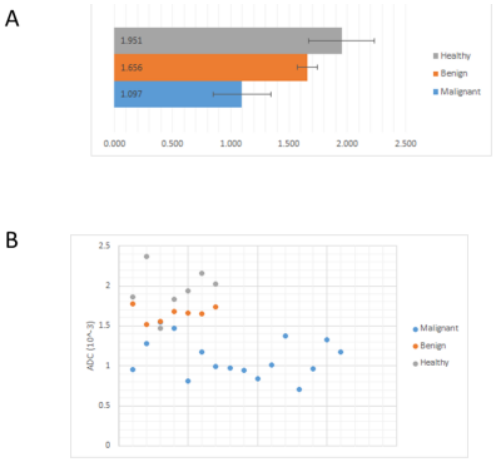

Figure.2: A) ADC values quantified from DWI of malignant and breast cancer patients and healthy women. B) Scatter plot showing the individual values of ADCs.

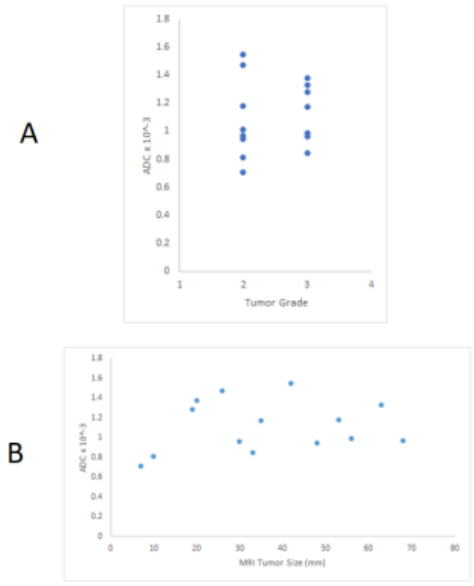

Figure.3: Plots showing ADC values versus A) tumor grades and B) tumor sizes.

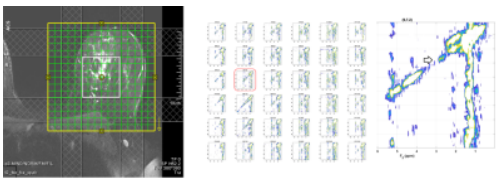

Figure 4. A) Axial MRI slice showing the field of view (FOV) with a yellow box and grids and the white box representing the volume of interest (VOI) localized by the 5D EP-COSI sequence(90^0_{ss}-180^0_{ss}-90^0_{ss}); B) Extracted multi-voxel COSY spectra from one of the slices; C) an extracted COSY spectrum marked in red color in B.

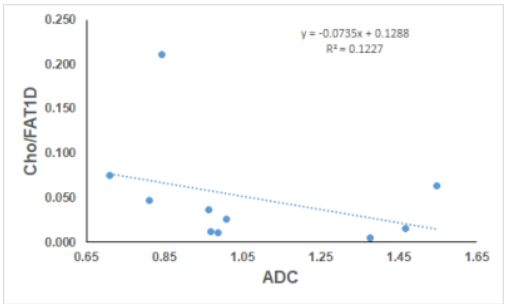

Figure 5. Correlation between the ADC values and Choline

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